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Attorney's Do. No. 4430-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Andrew D. Barofsky & Kenton W. Gregory

Serial No.: 08/797,770

Art Unit: 3738
Confirmation No. 1692
Examiner: Paul Prebilic

Filed: February 7, 1997

For: METHOD FOR USING TROPOELASTIN AND FOR PRODUCING TROPOELASTIN BIOMATERIALS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER FOR AMENDED APPELLANT'S BRIEF

An Appeal was taken from the Examiner's Office Action mailed September 11, 2002, rejecting claims 1-13, 15-24, 36-39, 41-55, 74, and 76-104 in this application.

An Amended Appeal Brief in furtherance of the Notice of Appeal was mailed in this case on November 5, 2002. This Amended Appeal Brief is filed in response to a Notification of Non-Compliance with 37 C.F.F. 1.192 mailed on May 28, 2003.

Applicant believes that no further extension of time is required, however if applicant has inadvertently overlooked the need for a petition and fee for extension of time, the Commissioner is authorized to charge any fees due to deposit account number 13-1703.

This Amended Appeal Brief is transmitted in triplicate.

Respectfully submitted,

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APPELLANT'S AMENDED APPEAL BRIEF UNDER 37 CFR 1.192 (d)

This brief contains these items under the following headings and in the order set forth below according to (37 CFR 1.192(c):

TABLE OF CONTENTS

I. INTRODUCTION

In furtherance of the Appeal Brief which has been reviewed by the Examiner, Confirmation No. 1692, dated 3/14/03.

This brief is in furtherance of the Notice of Appeal filed on November 5, 2002 and the Appeal Brief filed on January 6, 2003.

This is an appeal from the rejection, dated September 11, 2002, of claims 1-13, 15-24, 36-39, 41-55, 74 and 76-104 in the above-identified patent application.

The fee for filing the Amended Appeal Brief in support of the appeal under 37 CFR 1.17(f) was previously sent on November 6, 2002.

This Amended Appeal Brief is submitted in triplicate.

II. REAL PARTY IN INTEREST

The assignees of record of the full exclusive right, title, and interests in and to the above-identified patent application are Providence Health System-Oregon and Kenton W. Gregory.

III. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

IV. STATUS OF CLAIMS-37 CFR §1.192(c)(1)

A. Claims in the application are: 1-13, 15-24, 36-39, 41-55, 74 and 76-104.

B. Status of All the Claims:

1. Claims cancelled: NONE
2. Claims withdrawn from consideration but not cancelled: NONE
3. Claims pending: 1-13, 15-24, 36-39, 41-55, 74 and 76-104

4. Claims allowed: NONE

5. Claims rejected: 1-13, 15-24, 36-39, 41-55, 74 and 76-104

V. STATUS OF AMENDMENTS-37 CFR §1.192(c) (2)

All amendments that have been filed have been entered.

In the rejection dated September 11, 2002, claims 1-13, 15, 21, 22, 24, 74, 76-90, and 95-100 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-33 of co-pending Patent Application No. 09/000,604 (now U.S. Patent 6,372,228). Appellant asserted in the Appeal Brief that this issue should be handled outside this appeal.

The Appeal Brief has been reviewed by the Examiner. The Examiner in his review, Confirmation No. 1692, dated 3/14/03, states that the above-stated rejection under the judicially created doctrine of obviousness-type double patenting must be traversed or, alternatively, a Terminal Disclaimer must be filed in response thereto. Accordingly, a Terminal Disclaimer To Obviate A Double Patenting Rejection Under 37 CFR 1.321 (b) is filed herewith. In the aforementioned Terminal Disclaimer, Applicant disclaims the terminal part of any patent granted on the above-identified patent application, U.S. Serial No. 08/797,770, which would extend beyond the expiration date of the full statutory term of U.S. Patent Number 6,372,228.

VI. SUMMARY OF THE INVENTION-37 CFR §1.192(c) (3)

The subject invention of claim 1 is directed to a method for producing a biomaterial fused onto a tissue substrate. This method comprises providing a layer of the biomaterial consisting essentially of tropoelastin having a first and second outer major surface and a tissue substrate having a first and second outer major surface. (See Spec. page 11, lines 10-27)

In claims 2-9 (See spec. page 11, line 28 to page 12, line 26) an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, is applied to a selected one of the first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of the first and second outer surfaces of the biomaterial and one of the first and second outer surfaces of the tissue substrate. The energy absorbing material penetrates into the interstices of the biomaterial. The energy absorbing material is then irradiated with light energy in the predetermined wavelength range with an intensity sufficient to fuse together one of the first and second outer surfaces of the biomaterial and the tissue substrate. This fuses together the selected one of the first and second outer surfaces of the biomaterial and the tissue substrate. Preferably, this method further includes the step of indirectly irradiating the energy absorbing material by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material. The energy absorbing material can comprise a biocompatible chromophore. It can also comprise an energy absorbing dye. The method can further include the step of substantially dissipating the energy absorbing material when the biomaterial and the tissue substrate are fused together. Moreover, it can further include the step of staining the first or second surface of the biomaterial with the energy absorbing material. Preferably, the step of applying the energy absorbing material to one of the outer surfaces of the biomaterial is done by doping a separate doped biomaterial layer with an energy absorbing material, and then fusing the separate doped biomaterial layer to the biomaterial. The energy-absorbing layer is preferably substantially uniformly applied to a selected one of the first and second outer surfaces of the biomaterial, more preferably covering substantially the entire outer surface of the biomaterial with the energy absorbing material.

Furthermore (claims 10-13), as described on page 12, line 27 through page 13, line 14, the step of irradiating the energy absorbing material can be accomplished with light energy at a localized temperature of from about 40 to 600 degrees C. for period of time sufficient to cause fusing together of one of the first and second outer surfaces of the biomaterial and one of the first

and second outer surfaces of the tissue substrate. The tissue substrate can also be a live tissue substrate. The average thickness of the energy absorbing material, which penetrates into the interstices of the biomaterial, is preferably from about 0.5 to 300 microns.

More specifically, the method can further include the step of arranging the magnitude of the wave length, energy level, absorption, and light intensity during irradiation with light energy of the energy absorbing material, and the concentration of the energy absorbing material, so that the localized temperature at the interface of the first and second outer surfaces of the biomaterial and the tissue substrate are maintained at from about 40 to 600°C., thereby fusing together the biomaterial and the tissue substrate.

The method (claims 15-21) can comprise a tissue substrate which is selected from a group consisting of bladders, intestines, tubes, esophagus, ureters, arteries, veins, stomachs, lungs, hearts, colons, and skin. (See Spec. page 8, lines 7-15) It can further include the step of forming the biomaterial into a three-dimensional support structure wherein the biomaterial is combined with a stromal support matrix populated with actively growing stromal cells, preferably wherein the stromal support matrix comprises fibroblasts. (See Spec. page 9, lines 10-18) It can also include the step of forming a cellular lining of human cells on one of the major surfaces of the biomaterial layer, preferably wherein the cells which are employed to form the cellular lining are at least one of endothelial cells, epithelial cells and urothelial cells. (See Specs, page 10, lines 5-11) The method can also provide the step of forming an inner lining consisting essentially of tropoelastin for mechanical human structures to ensure their continued internal use in a human body, the inner lining preferably being formed in heart valves, heart implants, dialysis equipment, or oxygenator tubing for heart-lung by-pass systems. (See Spec. page 10, lines 12-17) In an alternative step, a drug is introduced into the biomaterial. (See Spec. page 14, lines 23-27)

Another method of this invention (see claim 23) can be provided for using a biomaterial as a tissue-fusible layer. (See Spec. page 11, line 10 to page 12, line 26) That method comprises providing a layer of biomaterial consisting essentially of tropoelastin having a first and second

outer major surface; providing a tissue substrate having a first and second outer major surface; and using the biomaterial as a heat fusible material by applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to one of the first and second outer surfaces of the biomaterial in an amount which will make the biomaterial tissue-fusible, and which will cause fusing together of one of the first and second outer surfaces of the biomaterial and one of the first and second outer surfaces of the tissue substrate, the energy absorbing material being applied so that it will penetrate into the interstices of the biomaterial. Again, the energy absorbing material is irradiated with light energy in the predetermined wavelength range with an intensity being sufficient to fuse together one of the first and second outer surfaces of the biomaterial and the tissue substrate.

In a further method (see claim 24) for producing a biomaterial consisting essentially of tropoelastin is fused onto a tissue substrate. (See Spec. page 11, line 10 to page 12, line 26) The method comprises providing a layer of the biomaterial having a first and second outer major surface and a tissue substrate having a first and second outer major surface, and applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to one of the first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of the first and second outer surfaces of the biomaterial and one of the outer surface of the tissue substrate, the energy absorbing material penetrating into the interstices of the biomaterial. Next, the energy absorbing material is indirectly irradiated by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material so that the light energy is in the predetermined wavelength range with an intensity sufficient to fuse together one of the first and second outer surfaces of the biomaterial and the outer surface of the tissue substrate. Then, one of the first and second outer surfaces of the biomaterial and the outer surface of the tissue substrate is fused together and the energy absorbing material is substantially dissipated when the biomaterial and the tissue substrate are fused together.

A method for producing a prosthetic device is described (claims 36-46), as set forth in Spec. on page 13, line 13 to page 14, line 22 which comprises providing a biomaterial layer consisting essentially of tropoelastin and a support member comprising a stent, a conduit or a scaffold. The layer of biomaterial is applied to the support member to form the prosthetic device. Preferably, the layer of the biomaterial is applied so that it surrounds the support member. The biomaterial can preferably be formed by polymerization, or molded into a suitable size and shape, or formed into a sheet or tube, and then covering the support member with the sheet or tube. It can also be applied to the support by grafting, or by mechanical bonding, or by laser bonding. A drug can be incorporated into the biomaterial layer thereby decreasing the need for systemic intravenous or oral medications. The support member preferably comprises titanium, tantalum, stainless steel or nitinol.

A method for producing a biomaterial can also be provided (claim 47). The method comprises providing a polymerizable monomer consisting essentially of tropoelastin. Then, the polymerizable monomer is polymerized to form a polymer consisting essentially of tropoelastin, which in turn is formed into a biomaterial consisting essentially of tropoelastin. (See Spec. page 8, lines 21-28) The preferred method (claims 51, 52 and 55) can include the step of forming a cellular lining of human cells and the introduction of drugs into the biomaterial, as set forth above. The biomaterial is preferably attached to a tissue substrate. Dependent claims 48-50, 53 and 54 are similar in scope to claims 15-17, 20 and 21.

A further method of this invention (claim 74) is for producing a biomaterial consisting essentially of tropoelastin joined to a tissue substrate. (See Spec. page 10, line 27 to page 12, line 1.) That method comprises providing a layer of the biomaterial consisting essentially of tropoelastin having a first and second outer major surface. Then, an energy absorbing material is applied to a selected one of the first and second outer surfaces of the biomaterial. The energy absorbing material is energy absorptive within a predetermined range of light wavelengths in an amount which will cause fusing together of one of the first and second outer surfaces of the

biomaterial and an outer surface of the tissue substrate. The energy absorbing material penetrates into the interstices of the biomaterial. The selected one of the first and second outer surfaces of the biomaterial is capable of joining together with the outer surface of the tissue substrate by irradiating the energy absorbing material with light energy in a predetermined wavelength range with an intensity sufficient to facilitate the joining together of the biomaterial and the tissue substrate.

In claim 76, an energy absorbing material is employed to fusing together the selected one of the first and second outer surfaces of the biomaterial and the tissue substrate. (See Spec. page 11, line 10 to line 27) Claims 77-97 which are dependent from claim 76, are similar in scope to dependent claims 2-13 and 15-22, respectively.

In claim 98, a method for using a biomaterial consisting essentially of tropoelastin as a tissue-fusible layer is provided. (See Spec. page 10, line 27 to page 12, line 1) This method comprises providing a layer of a biomaterial consisting essentially of tropoelastin having a first and second outer major surface, which is useable as a tissue-fusible material, and a tissue substrate having a first and second outer major surface. When an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, is applied to one of the first and second outer surfaces of the biomaterial in an amount which will make the biomaterial tissue-fusible, so that it will penetrate into the interstices of the biomaterial, it will cause fusing together of one of the first and second outer surfaces of the biomaterial and one of the first and second outer surfaces of the tissue substrate when the energy absorbing material is irradiated with light energy in the predetermined wavelength range with an intensity being sufficient to fuse together one of the first and second outer surfaces of the biomaterial and the tissue substrate.

In a method for producing an biomaterial fused onto a tissue substrate (claim 99) (See Spec. page 10, line 27 to page 12, line 1), a biomaterial layer consisting essentially of tropoelastin having a first and second outer major surface and a tissue substrate having a first and

second outer major surface is provided. An energy absorbing material is applied as described above. Then, the energy absorbing material is indirectly irradiated by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material, the light energy being in the predetermined wavelength range with an intensity sufficient to fuse together one of the first and second outer surfaces of the cross linked biomaterial and the outer surface of the tissue substrate. In this way, the energy absorbing material is substantially dissipated when the cross linked biomaterial and the tissue substrates are fused together.

In claim 101 a method is provided for producing a biomaterial from a monomer consisting essentially of tropoelastin. (See Spec. page 8, line 21 to page 9, line 9) The monomer is polymerized to form a polymer consisting essentially of tropoelastin, and the polymer is formed into a biocompatible biomaterial consisting essentially of tropoelastin. Then, a three-dimensional support structure is produced wherein the biomaterial is combined with a stromal support matrix populated with actively growing stromal cells. A method for producing a biomaterial is set forth in claim 103 which comprises providing a monomer consisting essentially of tropoelastin. (See Spec. page 8, line 21 to page 9, line 9) The monomer is polymerized to form a polymer consisting essentially of tropoelastin, and a biomaterial is formed from the polymer. A cellular lining of human cells is formed on one of the major surfaces of the biomaterial. (See Spec. page 10, lines 5 and 6) Dependent claim 102 and 104 are similar in scope to claims 17 and 19.

VII. ISSUES ON APPEAL-37 CFR §1.192(c)(4)

A. First Issue: Whether claims 24, 36-39, 41-55, 74, 76-98, and 100-104 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B. Second Issue: Whether claims 1-13, 15-24, 36-39, 41-55, 74 and 76-104 are unpatentable under 35 U.S.C. § 102(a) as anticipated by WO 96/14807 to Gregory et al ("Gregory, et al").

C. Third Issue: Whether claims 1-13, 15-24, 36-39, 41-55, 74 and 76-104 are unpatentable under 35 U.S.C. § 103(a) as obvious over Gregory et al in view of U.S. Patent No. 5,428,014 to Labroo et al ("Labroo et al ").

D. Fourth Issue: Whether claims 47 and 48 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Bedell-Hogan et al in the Journal of Biological Chemistry, page 1, lines 120-23 ("Bedell-Hogan et al ").

E. Fifth Issue: Whether claims 47, 48 and 53-55 are unpatentable under 35 U.S.C. § 102(a) as being anticipated by Labroo et al.

VIII. GROUPING OF CLAIMS-37 CFR §1.192(c) (5)

Claims 24, 36-39, 41-55, 74, 76-98, and 100-104 present the same issues on appeal under 35 U.S.C. § 112, second paragraph, and constitute one single group (Group 1).

Claims 1-13, 15-24, 36-39, 41-55, 74 and 76-104 present the same substantive issues on appeal under 35 U.S.C. § 102 (a) and constitute one single group (Group 2).

Claims 1-13, 15-24, 36-39, 41-55, 74 and 76-104 present the same substantive issues on appeal under 35 U.S.C. § 103 (a) and constitute one single group (Group 3).

Claims 47 and 48 present the same substantive issues on appeal under 35 U.S.C. § 102(b) and constitute one single group (Group 4).

Claims 47, 48 and 53-55 present the same substantive issues on appeal under 35 U.S.C. § 102(a) and constitute one single group (Group 5).

IX. ARGUMENTS-37 CFR §1.192(c) (6)

A. Rejections Under 35 U.S.C. § 112, second paragraph, of Group 1 Claims

Issue: Whether claims 24, 36-39, 41-55, 74, 76-98, and 100-104 can be rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. See Examiner's Action dated 9/11/02 (page 2). It is unclear why claims 1-13, 15-23, and 99 have not been rejected because these claims also contain the objectionable language "consisting essentially of".

The Examiner indicated that, for patentability purposes, he construed "consisting essentially of" in the claims as having the same meaning as "comprising". This construction is inappropriate upon a reviewing applicants' claims in light of the explicit prevailing law on the subject.

The transition language "consisting essentially of" has been held to render a claim open "only for the inclusion of unspecified ingredients which do not materially affect the basic and novel characteristics of the composition." Ex parte Davis, 80 USPQ 448, 450 (BPAI 1948); accord In re Herz, 190 USPQ 461, 463 (CCPA 1976); MPEP 2111.03. The Federal Circuit also has consistently recognized the meaning of "consisting essentially of", interpreting it to mean "exclude[ing] ingredients that would materially affect the basic and novel characteristics of the claimed composition". AFG Industries, Inc. v. Cardinal IG Co., 57 USPQ2d 1776, 1781 (Fed. Cir. 2001). The CAFC has left the claim "open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." Id. at 1781.

Applicants contend that the transitional phrase "consisting essentially of" is not confusing and indefinite and is in fact acceptable in form. See MPEP 2111.03. A biomaterial consisting essentially of tropoelastin can be produced using a cross linking agent which is substantially dissipated during the formation of that biomaterial. Fibrin and polypeptides are not synonymous

with tropoelastin and do not materially effect the structure of the biomaterial. Fibrin, polypeptides and cross linking agents are clearly precluded by the language "consisting essentially of". The Examiner has offered no evidence to the contrary. The Examiner's position that fibrin, polypeptides and cross-linking agents are all material to the structure of the biomaterial is totally unsupported by any actual evidence. The Examiner's view that the transitional phase "consisting essentially of" should be interpreted as having the same scope as "comprising" is totally without foundation and substantive support.

The Examiner has attempted to justify his construction of the transitional phrase "consisting essentially of" based on the possible presence of cross linking agents and other materials which are employed in the formation of the tropoelastin biomaterial (fibrin and polypeptides are not reactants or products of the formation of tropoelastin) after the tropoelastin biomaterial is produced. The tropoelastin product does not include any reactant which remains after polymerization has been completed.

The Examiner has asserted that the biomaterial layer of the claimed invention is not "consisting essentially of" tropoelastin. He then erroneously defines "consisting essentially of" as meaning the same as "comprising". This strained argument is contrary to prevailing case law, as well as the MPEP, which makes clear that the transitional phase "consisting essentially of" actually defines the basic and novel characteristics of the claimed invention. See PPG, 48 USPQ2d at 1355.

The specification recites several properties of the invention, including that tropoelastin "undergoes very little post-developmental remodeling or breakdown and is a relatively permanent connective tissue structure during the life of an organism." (Application, p. 19, lns. 7-8.) Tropoelastin biomaterials are further said to not elicit a foreign body reaction, and to provide relatively permanent, natural support matrices for organ and tissue reconstruction. The longevity and integrity of implanted tropoelastin also is asserted to be regulated by the host rather than environmentally-induced hydrolysis or enzymatic degradation of prior art materials.

B. Rejections Under 35 U.S.C. §102 of Group 2 Claims

Issue: Whether claims 1-13, 15-24, 36-39, 41-55, 74 and 76-100, and 103-104 are unpatentable under 35 U.S.C. § 102(a) as anticipated by Gregory et al. See Examiner's Action dated 09/11/02 (pages 3 and 4).

This application is a continuation-in-part of U.S. Serial No. 08/341,881, filed November 15, 1994 ("USSN '881"), and a continuation-in-part of USSN 08/658,855 filed on May 31, 1996 ("USSN '855"). USSN '881 is the parent application of the Gregory et al reference cited by the Examiner.

Applicants' have enclosed herewith the Declaration under 37 C.F.R. 1.131 of Cheryl L. Maslen, Ph.D. ("Dr. Maslen") and of Kenton W. Gregory, M.D. ("Dr. Gregory"). The Declarations of Dr. Maslen and Dr. Gregory establish and confirm completion of the invention in this application, in the United States, at a date prior to May 23, 1996. May 23, 1996, is the effective date ("Effective Date"), with respect to the above-captioned patent application U.S. Serial No. 08/797,770 ("Application"), of the prior art publication WO 96/14807 to Gregory, et al.

More specifically, Dr. Maslen was, as of the date of execution of her Declaration, an Associate Professor, Molecular & Medical Genetics and Medicine at the Oregon Health & Sciences University ("OHSU") and also Associate Director of the OHSU Heart Research Center,

both located in Portland, Oregon. Dr. Maslen conducted tropoelastin research at OHSU in collaboration with Kenton W. Gregory, M.D. and the Oregon Medical Laser Center ("OMLC") in Portland, Oregon. The tropoelastin research conducted in the OHSU laboratory of Dr. Maslen was funded entirely by Dr. Gregory at OMLC. Dr. Maslen clearly states that the work in her laboratory on tropoelastin began on or about September 1995, with the direct participation of Andrew Barofsky, a co-inventor in the above-referenced patent application, was undertaken by Mr. Barofsky, Dr. Maslen, and her laboratory personnel and students. The tropoelastin research, according to Dr. Maslen, was performed in her OHSU laboratory substantially continuously during the period of September 1996 to at least February 7, 1997. Furthermore, the tropoelastin research had continued to the date of execution of Dr. Maslen's Declaration, and beyond, without having been halted or abandoned for other research projects, lack of funding or personnel, or other administrative or financial reasons. Dr. Maslen confirmed that Dr. Gregory has supervised the tropoelastin research in her laboratory since its inception in 1995, and that she has made regular progress reports to Dr. Gregory at OMLC regarding the tropoelastin research. Dr. Maslen's regular progress reports have been included in reports made by Dr. Gregory and OMLC to the research grant sponsor.

The Declaration of Dr. Gregory supports the statements in Dr. Maslen's Declaration. Dr. Gregory's Declaration states that collaborative research was undertaken in Dr. Cheryl Maslen's laboratory at the Oregon Health & Sciences University (OHSU). An initial aim of the collaboration was to develop a tropoelastin expression system to provide quantities of tropoelastin to the Oregon Medical Laser Center (OMLC) for supporting Dr. Gregory's research at that location. Dr. Gregory substantiates that the work in Dr. Maslen's laboratory on tropoelastin began on or about September 1995, with the direct participation of Andrew Barofsky, a co-inventor in the present patent application, that work having been undertaken by Mr. Barofsky, Dr. Maslen and Dr. Maslen's laboratory personnel and students. Dr. Gregory goes on to state that the tropoelastin research was performed in Dr. Maslen's OHSU laboratory

substantially continuously during the period of September, 1996 to at least February 7, 1997 and, in fact, that this research has continued to date of execution of his Declaration. Dr. Gregory also verifies the fact that the tropoelastin research conducted in Dr. Maslen's OHSU laboratory was funded entirely by her research grant for tropoelastin. Finally, Dr. Gregory states that he has supervised the tropoelastin research in Dr. Maslen's laboratory since its inception in 1995, and that he has received regular progress reports from Dr. Maslen regarding this tropoelastin research. These regular progress reports from Dr. Maslen have been included in reports made by Dr. Gregory to the research sponsor.

A Declaration of Prior Invention in the United States to Overcome a Cited Publication under 37 C.F.R. 1.131 has also been presented to the Examiner. In that Declaration it is established that the invention of the pending claims was made at least by a date earlier than the effective date of the Gregory et al reference. The party making the Declaration is Dr. Kenton Gregory, the co-inventor of the above referenced application. Dr. Gregory is also one of the co-inventors of the PCT publication which is in fact the Gregory et al reference.

The Examiner further stated that no evidence was submitted to establish diligence from May 23, 1996 to February 7, 1997. Applicants assert that the exhibits to the Gregory Declaration contain evidence showing both engineering diligence and attorney diligence in preparation of the patent application. The evidence comprises the following dated entries in lab journals of inventors, Andrew Barofsky (AB) and Dr. Kenton Gregory (KG):

1. 5-23-96, AB book: under "Patent Ideas", remarks on "tropoelastin patent" (graft, stent covering, scaffolding uses);
2. 5-28-96, KG book: "Patent work -- tropoelastin";
3. 6-4-96, AB book: afternoon with JSM on "TPE patent";
4. 6-24-96, KG book: notes "Patent Tropoelastin -- Andrew is working on"
5. 7-11-96, AB book: states that "Jerry claims to have made progress adding stent stuff. . . should have a working final draft";

6. 7-18-96, AB book: "TPE claims";
7. 7-18-96, KG book: regarding "Tropo Patent", states that "Andrew to finish up on Marger most recent version";
8. 10-15-96, AB book: "Jerry M. on vacation -- was going to work on final draft over weekend."; and
9. 11-13-96, KG book: recites putting in "non-laser elastin applications claims" a list of things, including three "tropoelastin structure[s]" and several uses.

Copies of the lab journals of the inventors (numerically tabbed) are enclosed herewith.

Before and during the critical period, the Attorney for Applicants believes that he was exposed to evidence demonstrating diligent effort in advancing the preparation of the present application, such as conversations regarding the invention, prior art and drafts of the claims and specification, and that therefore, Attorney for Applicants believes that conception occurred, and that attorney-diligence became relevant, on or about May 16, 1996 through to February 7, 1997. It is also believed that the Attorney for Applicants prepared the present application and was in contact with Applicants routinely from a date prior to May 23, 1996 to the present, and that Applicants disclosed to the Attorney for Applicants the subject matter of the present application on or before the publication of the Gregory (WO) reference.

C. Rejections Under 35 U.S.C. §103 of Group 3 Claims

Issue: Whether claims 1-13, 15-24, 36-39, 41-55, 74 and 76-100, and 103-104 are unpatentable under 35 U.S.C. § 103(a) as obvious over Gregory et al in view of U.S. Patent No. 5,428,014 to Labroo et al. See Examiner's Action dated 09/11/02 (page 5).

Applicant's method claims 1-13, 15-24, 36-39, 41-55, 74 and 76-100, and 103-104 are described in Paragraph IV above. Gregory et al is an inapplicable reference for the reasons set forth in Paragraph VI. B. above.

Regarding Labroo et al, it is stated in column 4, lines 58-63, that the term "polymer" refers to a substance containing "two or more polypeptide monomers." The term "homopolymer" refers to polymers containing two of more "identical" polypeptide monomers. The term "copolymer" includes a polymer containing two or more "different" types of polypeptide monomers. In either the case of a homopolymer or a copolymer, as defined by Labroo et al, one or both of the polypeptide components must be a first polypeptide monomer which is a polypeptide monomer crosslinkable by transglutminase as described therein. In the case of a homopolymer, Labroo et al states that it is two of more of these first polypeptide monomers, and in the case of the copolymer it is this first polypeptide monomer and a second different polypeptide monomer. Tropoelastin is not taught or suggested for use as a first polypeptide monomer by Labroo et al. Tropoelastin is defined, in the disclosure of Labroo et al cited by the Examiner in Col. 9, lines 1-26, as one of a class of materials useful as a second polypeptide monomer, only in copolymer compositions, and only in combination with a first polypeptide monomer which is not tropoelastin. Tropoelastin is never disclosed or suggested as being usable as either a first polypeptide monomer or as a homopolymer component.

Moreover, Labroo et al, states in column 4, lines 58-63, that the term "polymer" refers to a substance containing "two or more polypeptide monomers." The term "homopolymer" refers to polymers containing two of more "identical" polypeptide monomers. The term "copolymer" includes a polymer containing two or more "different" types of polypeptide monomers. In either the case of a homopolymer or a copolymer, as defined by Labroo et al, one or both of the polypeptide components must be a first polypeptide monomer which is a polypeptide monomer crosslinkable by transglutminase as described therein. In the case of a homopolymer, Labroo et

al states that it is two of more of these first polypeptide monomers, and in the case of the copolymer it is this first polypeptide monomer and a second different polypeptide monomer.

Tropoelastin is not taught or suggested for use as a first polypeptide monomer by Labroo et al. Tropoelastin is defined, in the disclosure of Labroo et al cited by the Examiner in Col. 9, lines 1-26, as one of a class of materials useful as a second polypeptide monomer, only in copolymer compositions, and only in combination with a first polypeptide monomer which is not tropoelastin. Tropoelastin is never disclosed or suggested as being usable as either a first polypeptide monomer or as a homopolymer component. Labroo et al does not contemplate, suggest or teach the use of tropoelastin except as a second component of a copolymer the different first peptide monomers disclosed therein. Therefore, the requirements for anticipation have not been met by the Labroo reference with respect to the rejected claims.

The Examiner has introduced the concept of using tropoelastin per se as an "interchangeable" moiety with elastin, which is not specifically disclosed or taught by Labroo et al. This is pure speculation on the part of the Examiner which could have only been arrived at through hindsight reconstruction without any basis in the express teachings of Labroo et al (or Gregory et al even if it were available as a reference, which we posit it is not).

As stated above, Gregory et al is not a viable reference. Labroo et al does not contemplate, suggest or teach the use of tropoelastin except as a second component of a copolymer the different first peptide monomers disclosed therein. Therefore, the requirements for anticipation have not been met by the Labroo reference with respect to the rejected claims.

D. Rejections Under 35 U.S.C. §102 of Group 4 Claims

Issue: Whether claims 47 and 48 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by Bedell-Hogan et al in the Journal of Biological Chemistry, page 1, lines 120-23 ("Bedell-Hogan et al "). See Examiner's Action dated 09/11/02 (pages 5).

Claims 47 and 48 have been rejected under 35 U.S.C. § 102 (b) as being anticipated by Bedell-Hogan et al. The method comprises providing a polymerizable monomer consisting essentially of tropoelastin. Then, the polymerizable monomer is polymerized to form a polymer consisting essentially of tropoelastin, which in turn is formed into a biomaterial consisting essentially of tropoelastin. In order to have anticipation under 35 USC Section 102 (b), every element of the claim must be found in the prior art reference. A method for producing a biomaterial can also be provided (claim 47). This is not described in the Bedell-Hogan et al reference.

Claim 48 is a method for producing an biomaterial fused onto a tissue substrate, a biomaterial layer consisting essentially of tropoelastin having a first and second outer major surface and a tissue substrate having a first and second outer major surface is provided. An energy absorbing material is applied as described above. Then, the energy absorbing material is indirectly irradiated by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material, the light energy being in the predetermined wavelength range with an intensity sufficient to fuse together one of the first and second outer surfaces of the crosslinked biomaterial and the outer surface of the tissue substrate. In this way, the energy absorbing material is substantially dissipated when the crosslinked biomaterial and the tissue substrates are fused together. The tissue substrate is selected from a group consisting of bladders, intestines, tubes, esophagus, ureters, arteries, veins, stomachs, lungs, hearts, colons, and skin. This is not described in the Bedell-Hogan et al reference.

Therefore, the above rejection does not constitute prima facie anticipation under 35 U.S.C. § 102 (b).

E. Rejections Under 35 U.S.C. §102 of Group 5 Claims

Issue: Whether claims 47, 48 and 53-55 are unpatentable under 35 U.S.C. § 102(a) as being anticipated by Labroo et al. See Examiner's Action dated 09/11/02 (page 5).

In order to have anticipation under 35 USC Section 102 (b), every element of the claim must be found in the prior art reference. As stated above, Labroo et al does not contemplate, suggest or teach the use of tropoelastin except as a second component of a copolymer the different first peptide monomers disclosed therein. Therefore, the requirements for anticipation have not been met by the Labroo reference with respect to the rejected claims.

Claims 47, 48, and 53-55 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Labroo et al. In amended claims 47, 48, and 53-55, applicant has added the language that the biomaterial employed is "consisting essentially of " tropoelastin. In order to have anticipation under 35 U.S.C. § 102(b), each and every element of the claim must be found in the prior art reference. Labroo et al does not contemplate, suggest or teach connection of the use of tropoelastin except as a copolymer with a first peptide monomers as disclosed therein.

Therefore, the requirements for anticipation have not been met with respect to those claims by the Labroo reference. As an aside, it is also applicants' view that amended claims 47, 48, and 53-55 are also not obvious with respect to Labroo et al reference for the reasons stated above.

X. APPENDIX 37 CFR§1.192(c) (7)

The text of the claims on appeal are claims 1-13, 15-24, 36-39, 41-55, 74 and 76-104, as follows:

1. A method for producing a biomaterial fused onto a tissue substrate comprising:

providing a layer of said biomaterial consisting essentially of tropoelastin having a first and second outer major surface and a tissue substrate having a first and second outer major surface; and

applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to a selected one of said first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said first and second outer surfaces of said tissue substrate, said energy absorbing material penetrating into the interstices of said biomaterial;

irradiating the energy absorbing material with light energy in said predetermined wavelength range with an intensity sufficient to fuse together one of said first and second outer surfaces of the biomaterial and the tissue substrate; and

fusing together the selected one of said first and second outer surfaces of the biomaterial and the tissue substrate.

2. The method of claim 1, which further includes the step of indirectly irradiating said energy absorbing material by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material.

3. The method of claim 1, wherein said energy absorbing material comprises a biocompatible chromophore.

4. The method of claim 1, wherein said energy absorbing material comprises an energy absorbing dye.

5. The method of claim 1, which further includes the step of substantially dissipating said energy absorbing material when said biomaterial and said tissue substrate are fused together.

6. The method of claim 1, which further includes the step of staining the first or second surface of said biomaterial with said energy absorbing material.

7. The method of claim 1, which further includes the step of applying said energy absorbing material to one of said outer surfaces of said biomaterial by doping a separate doped biomaterial layer with an energy absorbing material, and then fusing the separate doped biomaterial layer to the biomaterial.

8. The method of claim 1, wherein the energy absorbing layer is substantially uniformly applied to a selected one of said first and second outer surfaces of the biomaterial.

9. The method of claim 1, which further includes the step of covering substantially the entire outer surface of the biomaterial with the energy absorbing material.

10. The method of claim 1, which further includes the step of irradiating the energy absorbing material with light energy at a localized temperature of from about 40 to 600 degrees C. for period of time sufficient to cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said first and second outer surfaces of said tissue substrate.

11. The method of claim 1, wherein the tissue substrate is a live tissue substrate.

12. The method of claim 1, wherein the average thickness of the energy absorbing material which penetrates into the interstices of the biomaterial is from about 0.5 to 300 microns.

13. The method of claim 1, which further includes the step of arranging the magnitude of the wave length, energy level, absorption, and light intensity during irradiation with light energy of the energy absorbing material, and the concentration of the energy absorbing material, so that the localized temperature at the interface of said first and second outer surfaces of the biomaterial and

the tissue substrate are maintained at from about 40 to 600 °C., thereby fusing together the biomaterial and the tissue substrate.

15. The method of claim 1, wherein the tissue substrate is selected from a group consisting of bladders, intestines, tubes, esophagus, ureters, arteries, veins, stomachs, lungs, hearts, colons, and skin.

16. The method of claim 1, which further includes the step of forming said biomaterial into a three-dimensional support structure wherein said biomaterial is combined with a stromal support matrix populated with actively growing stromal cells.

17. The method of claim 16, wherein the stromal support matrix comprises fibroblasts.

18. The method of claim 1, which further includes the step of forming a cellular lining of human cells on one of the major surfaces of said biomaterial layer.

19. The method of claim 18, wherein said cells which are employed to form said cellular lining are at least one of endothelial cells, epithelial cells and urothelial cells.

20. The method of claim 1, which further includes the step of forming an inner lining consisting essentially of tropoelastin for mechanical human structures to ensure their continued internal use in a human body.

21. The method of claim 20, which further includes the step of forming said inner lining in heart valves, heart implants, dialysis equipment, or oxygenator tubing for heart-lung by-pass systems.

22. The method of claim 1, which includes the step of introducing a drug into said biomaterial.

23. A method for using a biomaterial as a tissue-fusible layer, comprising:

providing a layer of biomaterial consisting essentially of tropoelastin having a first and second outer major surface;

providing a tissue substrate having a first and second outer major surface; and

using said biomaterial as a heat fusible material by applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to one of said first and second outer surfaces of the biomaterial in an amount which will make said biomaterial tissue-fusible, and which will cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said first and second outer surfaces of said tissue substrate, said energy absorbing material being applied so that it will penetrate into the interstices of said biomaterial,

irradiating the energy absorbing material with light energy in said predetermined wavelength range with an intensity being sufficient to fuse together one of said first and second outer surfaces of the biomaterial and the tissue substrate.

24. A method for producing a biomaterial consisting essentially of tropoelastin fused onto a tissue substrate comprising:

providing a layer of said biomaterial having a first and second outer major surface and a tissue substrate having a first and second outer major surface;

applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to one of said first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of said first and second outer surfaces of the

biomaterial and one of said outer surface of said tissue substrate, said energy absorbing material penetrating into the interstices of said biomaterial;

indirectly irradiating the energy absorbing material by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material, said light energy being in said predetermined wavelength range with an intensity sufficient to fuse together one of said first and second outer surfaces of the biomaterial and the outer surface of said tissue substrate; and

fusing together one of said first and second outer surfaces of the biomaterial and the outer surface of said tissue substrate and substantially dissipating said energy absorbing material when said biomaterial and said tissue substrate are fused together.

36. A method for producing a prosthetic device comprising:

providing a biomaterial layer consisting essentially of tropoelastin and a support member comprising a stent, a conduit or a scaffold; and

applying said layer of biomaterial to said support member to form said prosthetic device.

37. The method of claim 36, which includes the step of applying the layer of said biomaterial so that it surrounds said support member.

38. The method of claim 36, which includes the step of forming said biomaterial by polymerization.

39. The method of claim 36, which includes the step of molding said biomaterial of a suitable size and shape.

41. The method of claim 36, which includes the step of forming said biomaterial into a sheet or tube, and then covering said support member with said sheet or tube.

42. The method of claim 36, which includes the step of applying said biomaterial layer to said support by grafting.

43. The method of claim 36, which includes the step of applying said biomaterial layer to said support by mechanical bonding.

44. The method of claim 36, which includes the step of applying said biomaterial layer to said support by laser bonding.

45. The method of claim 36, which includes the step of incorporating a drug into said biomaterial layer thereby decreasing the need for systemic intravenous or oral medications.

46. The method of claim 36, wherein said support member comprises titanium, tantalum, stainless steel or nitinol.

47. A method for producing a biomaterial, which comprises:

providing a polymerizable monomer consisting essentially of tropoelastin;

polymerizing said polymerizable monomer to form a polymer consisting essentially of tropoelastin; and

forming a biomaterial consisting essentially of tropoelastin from said polymer.

48. The method of claim 100, wherein the tissue substrate is selected from a group consisting of bladders, intestines, tubes, esophagus, ureters, arteries, veins, stomachs, lungs, hearts, colons, and skin.

49. The method of claim 100, which further includes the step of forming a three-dimensional support structure wherein said biomaterial is combined with a stromal support matrix populated with actively growing stromal cells.

50. The method of claim 49, wherein the stromal support matrix comprises fibroblasts.

51. The method of claim 47, which further includes the step of forming a cellular lining of human cells on one of the major surfaces of said biomaterial.

52. The method of claim 51, wherein said human cells are selected from a group consisting of endothelial cells, epithelial cells and urothelial cells.

53. The method of claim 100, which further includes the step of forming an inner lining for mechanical human structures to ensure their continued internal use in a human body.

54. The method of claim 100, which further includes the step of forming an inner lining in heart valves, heart implants, dialysis equipment, or oxygenator tubing for heart-lung by-pass systems.

55. The method of claim 47, which includes the step of introducing a drug into said biomaterial.

74. A method for producing a biomaterial consisting essentially of tropoelastin joined to a tissue substrate comprising:

providing a layer of said biomaterial consisting essentially of tropoelastin having a first and second outer major surface; and

applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to a selected one of said first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of said first and second outer surfaces of the biomaterial and an outer surface of said tissue substrate, said energy absorbing material penetrating into the interstices of said biomaterial,

the selected one of said first and second outer surfaces of the biomaterial being capable of joining together with the outer surface of the tissue substrate by irradiating the energy absorbing material with light energy in a predetermined wavelength range with an intensity sufficient to facilitate said joining together of said biomaterial and said tissue substrate.

76. A method for producing a biomaterial consisting essential of tropoelastin fused onto a tissue substrate comprising:

providing a layer of said biomaterial having a first and second outer major surface and a tissue substrate having a first and second outer major surface; and

applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to a selected one of said first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said first and second outer surfaces of said tissue substrate, said energy absorbing material penetrating into the interstices of said biomaterial;

irradiating the energy absorbing material with light energy in said predetermined wavelength range with an intensity sufficient to fuse together one of said first and second outer surfaces of the biomaterial and the tissue substrate; and

fusing together the selected one of said first and second outer surfaces of the biomaterial and the tissue substrate.

77. The method of claim 76, which further includes the step of indirectly irradiating said energy absorbing material by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material.

78. The method of claim 76, wherein said energy absorbing material comprises a biocompatible chromophore.

79. The method of claim 76, wherein said energy absorbing material comprises an energy absorbing dye.

80. The method of claim 76, which further includes the step of substantially dissipating said energy absorbing material when said biomaterial and said tissue substrate are fused together.

81. The method of claim 76, which further includes the step of staining the first or second surface of said biomaterial with said energy absorbing material.

81. The method of claim 76, which further includes the step of applying said energy absorbing material to one of said outer surfaces of said biomaterial by doping a separate

biomaterial layer with an energy absorbing material, and then fusing the doped separate biomaterial layer to the biomaterial.

83. The method of claim 76, wherein the energy absorbing layer is substantially uniformly applied to a selected one of said first and second outer surfaces of the biomaterial.

84. The method of claim 76, which further includes the step of covering substantially the entire outer surface of the biomaterial with the energy absorbing material.

85. The method of claim 76, which further includes the step of irradiating the energy absorbing material with light energy at a localized temperature of from about 40 to 600 degrees C. for period of time sufficient to cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said first and second outer surfaces of said tissue substrate.

86. The method of claim 76, wherein the tissue substrate is a live tissue substrate.

87. The method of claim 76, wherein the average thickness of the energy absorbing material which penetrates into the interstices of the biomaterial is from about 0.5 to 300 microns.

88. The method of claim 76, which further includes the step of arranging the magnitude of the wave length, energy level, absorption, and light intensity during irradiation with light energy of the energy absorbing material, and the concentration of the energy absorbing material, so that the localized temperature at the interface of said first and second outer surfaces of the biomaterial and the tissue substrate are maintained at from about 40 to 600 °C., thereby fusing together the biomaterial and the tissue substrate.

89. The method of claim 76, wherein the tissue substrate is a live tissue substrate.

90. The method of claim 76, wherein the tissue substrate is selected from a group consisting of bladders, intestines, tubes, esophagus, ureters, arteries, veins, stomachs, lungs, hearts, colons, and skin.

91. The method of claim 76, which further includes the step of forming a three-dimensional support structure wherein said biomaterial is combined with a stromal support matrix populated with actively growing stromal cells.

92. The method of claim 91, wherein a stromal support matrix comprises fibroblasts.

93. The method of claim 76, which further includes the step of forming a cellular lining of human cells on one of the major surfaces of said biomaterial layer.

94. The method of claim 93, wherein said human cells are selected from a group consisting of endothelial cells, epithelial cells and urothelial cells.

95. The method of claim 76, which further includes the step of forming an inner lining of said biomaterial for mechanical human structures to ensure their continued internal use in a human body.

96. The method of claim 95, which further includes the step of forming said inner lining in heart valves, heart implants, dialysis equipment, or oxygenator tubing for heart-lung by-pass systems.

97. The method of claim 76, which includes the step of introducing a drug into said biomaterial.

98. A method for using a biomaterial consisting essentially of tropoelastin as a tissue-fusible layer, comprising:

providing a layer of a biomaterial consisting essentially of tropoelastin having a first and second outer major surface which is useable as a tissue-fusible material;

providing a tissue substrate having a first and second outer major surface; and

applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to one of said first and second outer surfaces of the biomaterial in an amount which will make said biomaterial tissue-fusible, and which will cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said first and second outer surfaces of said tissue substrate, said energy absorbing material being applied so that it will penetrate into the interstices of said biomaterial,

irradiating the energy absorbing material with light energy in said predetermined wavelength range with an intensity being sufficient to fuse together one of said first and second outer surfaces of the biomaterial and the tissue substrate.

99. A method for producing an biomaterial fused onto a tissue substrate comprising:

providing a biomaterial layer consisting essentially of tropoelastin having a first and second outer major surface and a tissue substrate having a first and second outer major surface;

applying an energy absorbing material, which is energy absorptive within a predetermined range of light wavelengths, to one of said first and second outer surfaces of the biomaterial in an amount which will cause fusing together of one of said first and second outer surfaces of the biomaterial and one of said outer surface of said tissue substrate, said energy absorbing material penetrating into the interstices of said biomaterial;

indirectly irradiating the energy absorbing material by directing the light energy first through the biomaterial or tissue substrate and then to the energy absorbing material, said light energy being in said predetermined wavelength range with an intensity sufficient to fuse together one of said first and second outer surfaces of the crosslinked biomaterial and the outer surface of said tissue substrate; and

fusing together one of said first and second outer surfaces of the crosslinked biomaterial and the outer surface of said tissue substrate and substantially dissipating said energy absorbing material when said crosslinked biomaterial and said tissue substrate are fused together.

100. The method of claim 47, wherein said biomaterial is attached to a tissue substate.

101. A method for producing a biomaterial, which comprises:

providing a monomer consisting essentially of tropoelastin;

polymerizing said monomer to form a polymer consisting essentially of tropoelastin;

forming a biocompatible biomaterial consisting essentially of tropoelastin from said polymer; and

forming a three-dimensional support structure wherein said biomaterial is combined with a stromal support matrix populated with actively growing stromal cells.

102. The method of claim 101, wherein the stromal support matrix comprises fibroblasts.

103. A method for producing a biomaterial, which comprises:
providing a monomer consisting essentially of tropoelastin;
polymerizing said monomer to form a polymer consisting essentially of tropoelastin;
forming a biomaterial from said polymer; and
forming a cellular lining of human cells on one of the major surfaces of said biomaterial.

104. The method of claim 103, wherein said human cells are selected from a group consisting of endothelial cells, epithelial cells and urothelial cells.

Respectfully submitted,
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Telephone: (503) 222-3613

By _____
Jerome S. Marger
Registration No. 26,480

3/28/95

Meeting w/ K. Gregory

Agenda:

① Kristy → Next step, characterization?
Cefuroxime, Any Antibiotic
Flourescence tagged

② Digest / stents update: Ready : Waiting

③ LNLL update: collaboration with Bass/Treat. / Patent: Tropoelastin Patches
Elastin/stent + paper, (Me) (write up)

④ Tropoelastin Papers / Production: Sleep on it. Need to consider when to pull the trigger

⑤ Science Paper: Very Articles, plots (spectrum)
↳ cell attachment sequences

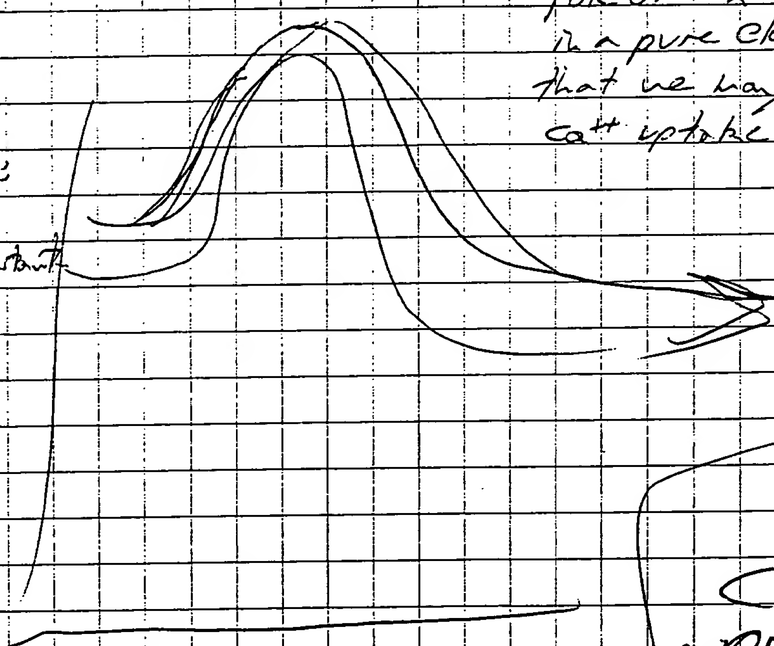
~~⑥ ASLMS:~~

~~⑦ USAMRMC discussion~~

Ken discussed the possible role of Ca++ and lipid deposition in a pure elastin stent. We concluded that we may need to incorporate Ca++ uptake inhibitors.

Weld testing:

What is important



Ca++ uptake Inhibitors
- processes
- Agents
- What does the body do

7/3/95

Meeting w/ K. Gregory

7/5/95

Sprint to Rob Hermes For Diamond Dusting!

Work on Elastin Patents (Ken has meeting on Weds, Thurs)

Have Erik work on suture tear test.

Make circular patch (digest) weld into coronary artery. (Lisa can help dissect out vessels)
Circumflex - no branches

Work on tester -

Work on paper -

7/24/95

Misplaced This Labbook. Found Today on Mickey's Desks.

Meeting w/ K. Gregory

Baculovirus - Ken is worried that insect cells may produce contaminants that are toxic, or antigenic.

Action Items

Ken needs copy of welding paper - (on disk or paper)

Send piece of Type I elastin, and digest to CNLL this week
Dennis Mathews
(510) 422-5360

Quantitate Biomaterial ; Weld Strength

Ken is meeting with Jerry Mayer on Tuesday morning ~1/2 hr to discuss tropoelastin patent.

1/2/96 Meeting with K. Gregory / A. Barofsky

Stent Implant: Dissection Ken & Lisa, photograph 35mm / Macro
1/3/96 Afternoon 3:30pm

New Course / Schedule? 35 hrs / wk.
4 cr. Molecular Genetics. only 1
Need to speak with Dr. Brennan.

Patent: Trying to finish up new examples.

Conferences / Trips: San Diego → Joan Zeltinger
Taos → Bioengineering
SPIE

→ Tropoelastin Patent
Need to get out ASAP →

→ Stents → practice deploying in Vitro

Meeting with K. Gregory

1/16/96

1) Henner – We can't section these types of stents.
Suggests stacking with scanning E.M.

no need to perfusion fix
rinse well with saline
dump into fixative.

2) Jerry Marger – → Welding Patent: examiner gave copy of
Oz international patent.

Tropoelastin: productive discussion on general
structure and content of patent.
I am making revisions now.

→ 3) Tropoelastin – Will begin library screening this week. – Aorta
→ Cheryl has skin fibroblast library. – Skin fibrob
Considering purchase of lung library (fetal) → $690
may be able to split costs.

T ; J Stent – We have one.

2/6/96 ~~Propoclastin~~ Meeting K.G. ; A.B.

Tropoclastin Patent - Ken wants 2hrs with Jerry Margon Thursday

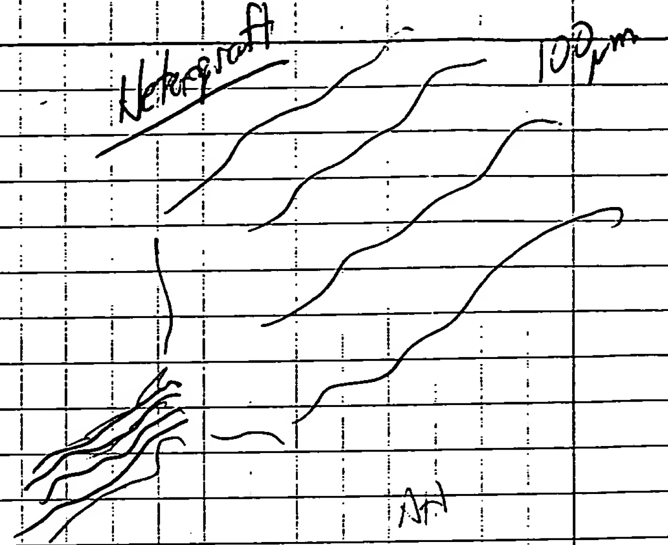
Covered Stents - Robert Virry From ACS needs: Specifications of Heterograft. (3:1 expansion) Thickness

we need balloons for animal delivery.

Johnson and Johnson - need copy of abstract (Circulation 1984) specs of Elastin scanning e.m. of before and after.

send To: Anthony Lunn
Director of Stent Therapeutics Research
J&J Interventional Systems
410 Technology DR.
P.O. Box 4917 Warren N.J.
07059

2/20/95



10 µm

- J & J, Robert Evry -

- Joan Zettinger -

Stent - ~ 10 µm

April 3, 4
May 1, 2

ATS - NH, AMA

Joan Zettinger - 551-1913
Fax 551-1917

- Paul Grasen - (619) 450-5723

Alana Wheeler - 450-5714

Action Items

Robert Evry - Contact, send graphs

&

J & J - Write Letter, send ~~materials~~ graphs,

Draft a letter -
- Purpose of Visit
- Field
- Dates

Patent - This Week, Finish

ATS -
10933 Torrey Pines
La Jolla
92037

619-450-6732

Next Week - The paper

Material Transfer Agreement - Steve Franey
Stephanie ?

3/12/96

Stent - letter to Bob Eury

Digesting small vessels.

- Sterilization - Send stents to γ-irradiation facility in CA

Patent - Stent Patent - corrections/revisions

Tropoelastin - Jerry has not sent me a draft.

Action Items

CCD Camera - ~~Any~~ Does chery/ have any use.

Flourescence - ~ gadgets systems etc.

ATS - Visit look for grips/ -

ATS

Action Items:

Animal Implant - 6-10 by May 5

- call ATS
- CCD camera
- Digest Vessels (Take to OR's tomorrow)

1) Method to secure elastin on stent →

2) Method to deploy →

3) More stents - call Bob

4) Pigs ordered and scheduled

5) Detailed protocol and analysis — Thrombosis/platelet adhesion

100

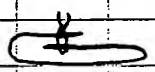
3/26/97

- Patent Review - Welding - Ken's Comments back to Jerry.

  Stent - I need to get.

  Tropelastin

- STents, ~~AIS~~ ACS Try suturing.



- Bacterrus - ~~TS~~ Order cells, Cheryl is ready to get started.

- Cold Springs Harbor → Biology Lab

  Biomaterials Society ⇒ Joan Z can help/recommend.

- ATS visit - Have we heard anything.

  Call Paul Gruen ask about letter.

Armed Forces Grant Personal Development - Liz, Ken, Andrew

4/9/96 Meeting With Ken.

Stent Experiment: Afternoon after Mtg. w/ Lisa
(I need to call Rob Eury.)

ATS Visit:

Patents: Sent Illustrations to Jerry.

✓ Call Jerry

Working on Dates and Times for ✓ Microbiology Lab techniques course. — ✓ June

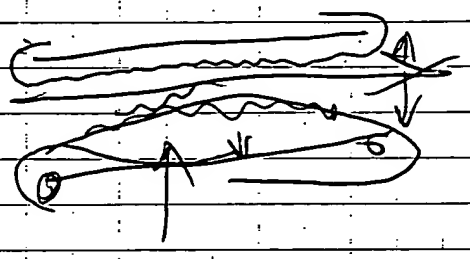
Hong Ming? - Call - wants to set up baculovirus system - large scale protein.

4/23/96 Meeting With Ken.

Stents: Richard Reposa Sewing 20

Patents: ? Call Jerry Marger.

Heterograft Testing: Go Back and test. Do not pull to force



5/16/16

Meeting w/ J. Mansour.

End-Use:

1) method of making a x-linked ~~pol~~ material ⇝ prior art

2) method of using.

3) Product ⇒ x-linked material.

End Use ⇝ what do we have?

1) scaffold ⇒ endothelial fibroblast epithelium

3) Graft ⇒ vascular skin

4) Addition to a graft.

1) Uses for tropoelastin matrix from - mother patent / stitch patent.

2) Description Includes Baculovirus expression and crosslinking.

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5/21/96

Action Items:

- Work on manuscript →
- Get Implanted Stents to Kenner →
- Mice Implant Protocol -
  Processing Methods.

5/23/96

Patent Ideas

Tropoelastin → Graft, stent covering, substrate for welding as described in mother's stent patents.

Scaffold For Fibroblast Growth, Keratinocyte Growth, (Skin or Vascular) SMC Growth.

Substrate for Endothelial Cell growth.

Heterograft → Scaffold For Fibroblast Growth, keratinocyte Growth, SMC growth.

Substrate for endothelial Growth.

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5/28/96 Mtg. w Ken.

Stents: Package and ship to Reno Vermin.

Patent: Schedule Mtg. w/ Jerry Mayer → Strategize.

New Idea - Elastin as cosmetic implant -

#1 project - Patents.

Kristy's New Students:

Kristy ⇒ work on bio materials
mice implant

New student ⇒ Lisa, testing.

6/4/96 Meeting with Ken.

3

- ✓ - Package ~~this~~ stents right away ⇒ get ~~Reno's~~ Address.
- ✓ - Elastin Stent Patent is finished!
- ✓ - T.P.E. Patent: Spend afternoon with Jerry. Cosmetic CIP → Add to TPE, Mother
- Payer - Ken will keep a working copy ~~of~~ on Portable Mac.

Schedule meeting with: Bernie Fox. Implant Studies.
Kristy.
Andrew.
Ken.

- ✓ - Work with Ursula on Research Associate Job Description.
Customize Description → get to Ken.

6/4/96

Renu Virmani
Armed Forces Institute of Pathology
Dept. of Cardiovascular Pathology
6825 16th St., Bldg 54, 2005
Washington D.C. 20306-6000
(202) 782-2844

Stents From animal implant sent:

4/24, 4/25, 4/26, 4/29, 4/30

√

4/29 already (covered)
dissected open

6/11/96

- Schedule Mtg. Bernie Fox — Ken Leaves next thursday @ Providence
  Kristy Nanna
  Andrew
  Ken
- List of Equipment @ ONSV
- Tell Cheryl - Ken orb o= Elastin Money.
  Darci
- Patents (TPE) - Andrew - Fibroblast ⇒ Ceb ATS patents from Jerry
  Ken - Cosmetic

1) Patent : TPE → Jerry claims to have made progress adding more stuff. I have a few corrections to make, → should have a worthy final draft.

ATS - haven't heard anything

2) Stents - We have 6 left.
Need to better define our benchtop experiments

Issues:
- Expand 2-3 mm Artery.
- 4-3 in vitro ?

Ron Virmani ~ Where are our stents.
call Ron?

3) Dermal Implants - Bernie called me and left a message
mice should be here next week?
He ordered them on his money for now.
Kristy and I will work out processing details.

4) Dr. Schwartz - Wants to do Urology (see previous page)

Comments?
Confidentiality agreement

5) Baculovirus - Making progress.

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7/18/96 Meeting with Ken.

→ Patent: ~~TPE~~ Claims → Fibroblast Culture? ATS

→ Biomaterials Engineer Advertisement: Journal of Biomaterials
- Work on Advertisement.

→ Dermal Implants: Meeting with Eric & Kristy today } Need Results
Mice should beat Providence. } From H-graft testing.

[Friday, A.M. 9:00 Biomaterials Mtg.] → Kristy, Mark, Ken
Andrew, ~~Scott~~ Steve?
Lisa

→ Heterograft Testing: → Vessels at Heniers for histology.
- Scanning EM, Blocks.
Transmission

★ To Items: Interpret Test Data
Look at Nist
↳ Send Best Samples for A.A. analysis, Scanning EM, Transmission EM.

ATS - Visit ~ 2-3 weeks
- Confidentiality is signed -

- Elastin Graft - Plan of Action -

Patent: Schedule 2 hrs. with Jerry to get it done!

- Schedule Work Meeting w/ Cheryl, Darcie, Rob, Andrea, Ken. about TPE part of grant.

- Set up Biomaterial Database → summarize findings.

- Call Carlton about setting up prices, Guaranteed purchase every month. Call Karen about ~~setting up~~ sending more money.

- Set up dissecting scope for taking pictures OR storage specimens.

10/15/96

Meeting w/ Ken

1) ATS - Jana Sipes, MTA →

2) Patents JM.

3) TPE - 1 1/2 yrs. before Implanting
need to hammer out broad milestones.

4) Put 45 min. in schedule for Andrew's Letter.

10/17/96
Apr

- Meetings : Biomaterial — Hilton Head.
New Orleans.

ICG Deposition / Welding.

Stability, Formulation, Spraying, Soaking etc.

Printing Techniques
Stamping -
Rolling -
Spraying;

Stents; Cover our last ones
Glue } expand
Weld }
maybe try thin material.

Action Items : - Order Small Vessels from Carlton
~~on Mo~~ for Monday, digest use for stent
covering.

- Soak patches in ICG, ICG Albumin,
See if it is absorbed (for Dr. Schwarz).

- Tomorrow, digest vessels so we can
have some HGs to use for ICG deposition
studies.

Get Ready to set up storage studies w/ NS.

Strain-Rate –

$\sigma = C\varepsilon^m$ m = Strain Rate sensitivity.

↑ stress

$$\sigma_2/\sigma_1 = (\varepsilon_2/\varepsilon_1)^m$$

$$m = \ln(\sigma_2/\sigma_1) / \ln(\varepsilon_2/\varepsilon_1)$$

10/15/96 Weekly meeting with Ken.

1) Patent: - Jess/ M. on vacation.
- was going to work on final draft over weekend.

2) ATS: MTA is good.
Materials vs. Modified materials.
Limit exposure of apps. to smallest possible groups.
Cannot show modified materials to anybody w/o confidentiality disc.

3) Abstract: need to design experiments.
cardiovascular.

Department Oregon Medical Laser Center

Subject Research

Name Keaton Gregory 9/6/94-

Address

National Brand 43-648

Computation Notebook

Dennison Stationery Products Co., Framingham, MA 01701

0 73333 43648 8

75 Sheets
11¾" x 9¼"
4x4 Quad.

5/14/96 Elution - Andrew

Manuscript current copy -

Tropo Elution Patent

Stat Patent - Andrew review then Ron G review.

Implanted Stents - Call Rao Virmani re scanning EM.

Andrew - Call ACS - "We implanted 4 stents and no acute thrombosis. The scanning is pending

Andrew - write up Elkins paper but our paper first.

8/20/96 Elastin Meeting c̄ Andrew

Send Acute in vivo elastin skinned stents to Renu Virmani via Fed Express

Patent Work

✓ Mitra Patent 2

Schedule meeting c̄ Jim Maya ✓ Elastin covered stent — Ken review.

Tropo Elastin —

Fibroblast encorporated Elastin Biomaterial

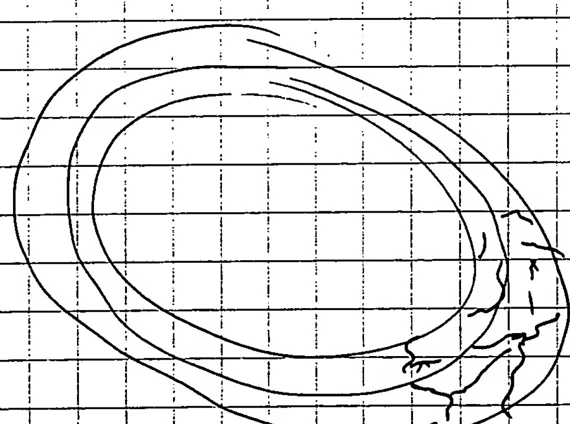
Cosmetic Application

Manuscript

Christie Hanna — will make quantities of Biomaterials

will work on mouse antigenicity study

Plan in vitro covered stent experiments.



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1/4/12 Andreas Elektra

✓ need to send stats to Ken

- To build Tropo Elektra start

To work on manuscript. - Ken

O Finish blast patent

✓ Mission list - Darci to start work on Elektra Grant

✓ Ken - call Steve F re indirect rate.

O Andrew schedule meeting w KG AB B. Fox C. Herman re: movie protocol

Also... patent ideas on Elektra production ie

4

6/24/96 Elastin meeting c̄ Andreas.

ATS confidentiality docs finalized

Renu — nothing sure

ACS — no response.

→ Covered stents — put some in in vitro

meeting c̄ Bernie F to get more markers

Patent — Tropo Elastin — Andreas working on

Patent — Fibro blast incorporation.

Mark Wagner here to study tensiometer at whole graft

7/14/96 Elastin - Andrew

Fibrin starts in arteries in vitro

- Trapo patent almost ready
- Fibroblast encapsulation
- ATS - did the contractility go out

→ Test heterogeneity - diameter
elasticity - media wasn't
and then put on and expand
and see if you can eliminate intra-strut
narrowing.

Primed implants - mice ordered
protocol approved
practice needle implants in vitro
must ensure that elastin is in needle.

Andrew's promotion & research associate - in.

Andrew call Rino Virmani.

Dr Jerry Schwartz - bladder tack-up procedure.
visited lab & Andrew.
needs better laser / optical appliance.
get a patch.

Get samples of tissues he wants to work
and then work the tissues - he
will do in Monkeys.

Meet & Jerry Mayer re Fibrin - Fusion Patent

7/18/92 Elysha c Andrew

Heterograft —

→ Mark Wagner has new results

Finalized heterografts - prior to closing [illegible]

⇒ amino acid analysis

⇒ scanning / Transmission EM

→ stress strain analysis.

ATS — Andrew will go c me to LaJolla.

Tropo Patent - Andrew to finish up

on Marge's most recent version.

Schedule Biomedical Group meeting.

Working on Fitting stents c elastin sleeves.

1st Quarter AFG Task List

Biomaterials

Biopolymer - Tropoelastin Expression

Heterograft

- storage media
- Intradermal implant

Application-specific processing

Biomaterial (Intestine Path)

Antibiotic Incorporation

Optimization
- strength
- flexibility

Dye Deposition

- Staining / Resisting
- Fluxing - Fibrinogen
- Membrane

Optical characterization

Dye stabilization

Storage

Processes
- Printing / Litho

Other Dyes

Laser Fusion

Mechanisms

Thermal History
- characterization
- modelling

Tissue Considerations
- Hydration
- Temp

Pressure Effects

Mechanical Considerations

Perameter Optimization

Specific Application
- ureter, cartilage etc

Biomaterial Delivery
- Appliances / Techniques

Laser

ster

out sourcin

Optical

Recruit

9/3/94 Electron - Andrew

Mat Trans Agreement - Request back to ground - sent to AB.

AA analysis - set soln

storage expt - underway.

Mock protocol - set going

Dopa - Potent - Reading

Pepa - - Reading.

Schedule Biomaterials group meeting.

Work on stent covering.

ECG deposition studies.

9/6 Elaitis - Andrew

→ MTA to Tanna Sipes

→ Promotion being worked on by Stu E

→ Schedule 2 hrs E Jerry Mayer

→ AB to schedule OHSU mikel grant meeting
e. establish funding equipment personnel
plan, reporting plan, milestones
make adjustments etc.

→ Need Mike Wagner's final report.

→ Storage experiment

→ Data base on Biomatrix — findings
- simple summary of experiments — reference
(cs not back pages.

→ What about getting a deal from Carlton?
R. hips — guarantee a certain number per-
month so they can schedule harvest

?/7/96 Andrew B. - Elastin

- Meetings - Annual Biomaterials group

UHSV - growing cells nicely - need gene library
- Karen E to order.

Andrew - hasn't gotten reide

Andrew to work on ELG deposition
& welding.

Stent covering -

10/17/96 Biomaterials Group

Tensile Testing Book — Buy it

Christie to set up 35 mm camera on implant for fluorescent studys.

Department OMLC

Subject Laser/Biomedical Expt

Name Kenton Gregory

Address 10/22/96 –
9155 SW Barnes Road
Portland Oregon 97225

National® Brand

Computation Notebook

11 3/4" x 9 1/4", 4 x 4 Quad., 75 Sheets 43-648

503 216 2109

0 73333 43648 8

AVERY DENNISON

Office Products
Chicopee, MA 01022

mich 11/27/96

CONFIDENTIAL

November 13, 1996

To: Jerry Marger, Andrew Barofsky

Re: Tropo-Elastin patent Application Claims

Jerry;

We need to put in the non-laser elastin application claims

A tropoelastin structure

A tropoelastin structure that has a cellular lining of human cells-autologous or otherwise-endothelial, epithelial, urothelial

A tropoelastin structure that is populated with fibroblasts endothelial and other cells as needed to make a living structure to be implanted

Individual applications

Bladder, Ureter, artery, vein, esophagus, stomach patch, intestinal or colon patch, artery patch ie for aneurysm, esophagus patch for esophageal varicies, a patch for congenital or other cardiac repair, skin, cosmetic implant-intr-dermal, breast implant, solid organ patch, lung patch so it will be compliant and stretch

a biocompatible ling for heart valves, heart implants, or even idalysis or oxgenator tubing for heart-lung bypass

A fallopian tube replacement or repair

Baldder neck suspension or means of restoring tissue such that normal architectural relationships are re-established to promote urinary continance

Drug encorporation-add PDT agents

Do we want to describe optical appliances for energy delivery?

other delivery appliances?

dextrose or glucose etc bullets for deployment?

ICG that has been pre-measured for absorbance so that a precise amount of light is delivered

Kenton Gregory, M.D. Ken

67 Andrew B.

Reviewed patent drafts - election

Tropo, Biomaterial aff's, Divisions

SPIF Pyr -

Pat is for welding, slides

Dye - Targeted Laser Fusion - Pulsed Laser -

- Diat ICG fusion stronger than

solder - based fusion.

Patch welding - c Pulsed Laser -

solders inferior.

1/25/97 A. Banchs[?]

— Priorities

#1 Elastin Paper

#2 Welding → Pre-animal studies

#3 Development of TropoElastin

4. Calcification heterograft development.

Need to look at overlap microscopy for laser fusion

- Andrew knew how to look at collagen birefringence for thermal injury.

- to go to store/mgr for -lc/Rx.